is of one piece, with a smooth process throughout. The clear implication is that there is no delay in the onset of action, either of the active drug or of the placebo. By using the slope of the graph, one can use all of the trial results, not just those on a particular day. The statistical power is greatly increased and the distinction between drug and placebo enhanced.

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Author's reply I thank Professor Priest for further insights concerning the difficulty in obtaining sufficient statistical power to distinguish the early drug–placebo response. This is correct but the reason for the difficulty is mainly that the absolute difference between drug and placebo is initially small and when combined with typically low sample sizes the overall power to detect a true difference is insufficient. That said, if the aim of the study is to discover how early an effect is manifest there is no alternative to regular early measures.

Professor Priest then anticipates our next piece of work to which I previously eluded – examination of the trajectories of antidepressant response. He quite cleverly observes that a comparison of the slope of the response curves for the active drug and placebo is in effect a test of efficacy. It is also suggested that the response is often neither delayed nor steady but actually rapid (or perhaps more accurately 'accelerated'). Allow me to illustrate this point further (Fig. 1). The rate of change of those taking placebo is poor compared with a hypothetical antidepressant with a 'steady' or 'rapid' onset. A delayed onset, as so often suggested, is not illustrated, but I expect readers will be able to sketch their own view of the delayed trajectory. In fact several 'delayed' paths are possible, depending on whether there is a catch-up with the steady path and if so, when.

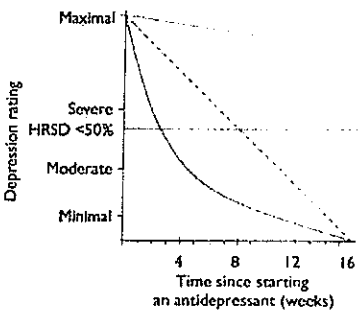

Fig. 1 Depression rating against time since starting hypothetical antidepressant with rapid (—) and steady (- - -) onset. HRSD, Hamilton Rating Scale for Depression; · · · · · · , placebo response.

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Primary agoraphobia as a specific phobia

The elegant study of 1920 participants from the Baltimore Epidemiologic Catchment Area programme concluded that 'the implied one-way causal relationship between spontaneous panic attacks and agoraphobia in DSM–IV appears incorrect' (Bienvenu *et al*, 2006). Bienvenu *et al* echo the arguments of many researchers, beginning with Marks (1987), that agoraphobia without panic attacks (primary agoraphobia) should be reinstated in DSM–V as a stand-alone diagnosis as in ICD–10.

It has been argued that evolutionary biological reasoning predicts the existence of a 'hard-wired' primary stand-alone agoraphobia, which should be classified with other specific phobias (Bracha, 2006). Specific phobias have been considered as conserved traits that enhanced survival during the human era of evolutionary adaptedness (Nesse, 1999; Bracha, 2006). Primary agoraphobia may similarly be traced back to the fact that humans relied on arboreality as a major escape response long after they diverged from chimpanzees. *Homo sapiens* expanded beyond its densely forested East-African indigenous niche into sparsely wooded habitats (savannahs and water-front dunes) only about 70 000 years ago. In sparsely wooded habitats, anxiety in wide-open spaces was arguably a survival-enhancing trait since opportunities for arboreal escape from large predators were limited (Bracha, 2006). These arguments may be relevant to psychiatric classification and contribute to the 'neuroscience research agenda to guide development of a pathophysiologically based classification system' emphasised in the research agenda for DSM–V (Kupfer *et al*, 2002).

If, as one of us (Bracha, 2006) has argued, the two types of agoraphobia have different modes of acquisition, there might be some clinical implications. Primary agoraphobia might, like other specific phobias, be especially amenable to virtual reality exposure treatment. In contrast, agoraphobia secondary to panic attacks can be classified in DSM–V and treated along with post-traumatic stress disorder (and other fear–memory–overconsolidation disorders, which are misclassified as specific phobias in DSM–IV–TR, e.g. hospital phobia, dentist phobia, dog phobia, bird phobia, and bat phobia).

Finally, contrary to myth, predictions based on brain evolution are eminently testable/falsifiable (Nesse, 1999). Some 30 such predictions are elaborated elsewhere (Bracha, 2006).

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Authors' reply We are grateful to Bracha *et al* for their interesting comments regarding primary agoraphobia as a potential evolutionary adaptation. First, we should clarify that we did not propose an additional diagnostic category; rather, we proposed that agoraphobia itself should be a stand-alone diagnosis in DSM–V (as in ICD–10), like other phobias. Subdividing what has historically been called agoraphobia may be useful, but we are concerned that clinicians and researchers are adopting Klein's narrower conceptualisation of agoraphobia as simply fear of panic in typical agoraphobic situations (Klein, 1980), without considering the possibility that a broader conceptualisation may be useful. Epidemiologists are increasingly adopting the definition of agoraphobia as 'fear of fear' (e.g. Grant *et al*, 2006), rather than the broader fear of difficulty in escaping, etc., in characteristic situations. As noted in our article, what has historically been called agoraphobia is strongly but not exclusively associated with panic, and, when the association exists, agoraphobia is not always preceded by panic.

The concept of an evolutionary basis for the development of phobias is not new (Seligman, 1971; Marks, 1987). Nevertheless, the reasons why people with agoraphobia develop fear and avoidance of particular situations remain important. Bracha *et al* suggest that fear of open spaces is an evolutionary remnant of primates' use of trees to escape from predators. However, although some people with agoraphobia are fearful of open spaces, the list of typical agoraphobic situations is broad (Marks, 1987). Thus, hypotheses with an evolutionary basis to explain agoraphobia will be expected to cover reasons why persons fear and avoid a variety of situations. Although it is difficult to 'prove' such hypotheses, we agree with Bracha *et al* that researchers can make falsifiable predictions that can continue to illuminate the field.

We agree that cognitive–behavioural techniques may be particularly important for persons whose agoraphobia is primary. However, many people with agoraphobia can benefit from such treatment, whether the syndrome is primary or secondary (Klein, 1980).

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One hundred years ago

Remorse in melancholia

REMORSE – that most poignant emotion – has often been depicted for us with a wealth of imagery in words which raise it at once to the chief place in human suffering. It has been described as the biting of teeth which, once fleshed in sin, now tear the heart of the evil-doer, of whom it has been written that "terror "takes hold on him as waters and a tempest stealeth "him away in the night"; as the torment of a galled conscience; as "a still baking oven, another hell"; and as the overwhelming revulsion of feeling loosed by

> The print and perfume of old passion,
> The wild-beast mark of panther's fangs.

But, wherever described by writers unversed in modern psychology, it will be found that this exquisite moral pain is attributed solely to a realization of the shortcoming of some actual conduct, as compared with ideal standards of behaviour, founded on logical concepts of good and evil – that is, to an intellectual judgement. This conception, implicit in most religions, is still held by the commonality of people, and is, further, firmly maintained by some important intellectualistic schools of philosophy, for whom such terms as "conscience," "morality," and "moral sentiment" connote simply and entirely rational processes or states. Opposed to this Kantian conception of morality are the views of those who maintain that moral reactions are determined, not only by the voice of reason, but by the effective or emotional character; that conscience is not an omnipresent, infallible guide to conduct, identical in all men, but that it varies in different people, and even fluctuates in the individual himself, according to the state of his mental and emotional poise, or what Janet has called the *niveau mental*.

By implication, the pain which accompanies a retrospective view of immoral acts should vary according to effective and physiological conditions. Now it is evident that in introducing here the word "physiological" one assumes a causal nexus between physiological conditions, such as, for example, intravascular tension, heart beat, excretory elimination and neurotrophic functions on the one hand, and the effective elements which contribute to the production of such moral feelings and sentiments as joy, anger, fear, sympathy and hate on the other – an assumption which the intellectualists, who regard the somatic phenomena as consecutive and reflex, would say simply begs the whole question. Notwithstanding, however, the inherent difficulty of analysing the emotions, it may be fairly stated, we think, that probably most psychologists, and certainly the majority of alienists to-day, are supporters of the